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A Theoretical Explanation on Neural Regeneration and the Science Behind the Brain's Refusal to Heal

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ABSTRACT

The Animal Kingdom consists of a variety of organisms that each have a unique regeneration process for organs and the function of the body. For instance, among vertebrates, the capacity of brain regeneration works on a whole new level than it does for mammals. An example of this vertebrate includes a Zebrafish, a teleost with a relatively simple neural system and structure, that can regenerate an extensive amount of its brain regions even after injury, including areas that are analogous to the mammalian forebrain. – In neuroscience, it is common to compare the analogous brain structures across different classes; so even though vertebrates and mammals are two different classes, the analogous forebrain regions may share development pathways. The neural stem cells multiply, damaged circuits are regenerated or reformed, and behavioural functions can possibly be restored. In contrast to this phenomenon, when an adult human brain is injured, suffers trauma or undergoes a stroke, it responds by protecting the damaged brain area by inflammation, gliosis or isolation, forming scar tissues, rather than processing regeneration – due to this, new neurotic signals are not formed, the broken connections between the damaged neurones are not repaired and the lost brain function is generally permanent. Additionally, even though the human brain is incapable of regenerating itself after injury, the genetic instructions needed to build brain tissues are still present in our DNA. This could mean that the ability of the brain to repair itself is not entirely missing – instead, the gene may be turned off or tightly controlled. When this process of regeneration is compared with species that are capable of doing this, it is evident that regeneration does not primarily focus upon having the right genes, but it is about how these genes are regulated in each species. In this paper, we explore the possibility of how the human brain may be deliberately limiting its own healing ability. This could be looked at as a protective strategy rather than a flaw, a strategy that aims to preserve complex functions – like memory, personality, and consciousness.

Keywords: *Brain Regeneration, Central Nervous System, Glial Scarring, Hippocampus, Identity, Neural Progenitor Cells, Non-Neurogenic Zone, Subventricular Region.*

1. RESEARCH QUESTION

What could prevent the adult human brain from carrying out functional regeneration post-injury, despite having the ability to retain the genetic capacity required for repair?

2. INTRODUCTION

The human brain is remarkably one of the many complex and functionally important organs – managing memory, consciousness, language, and identity through a network of neurones and glial cells. Nonetheless, despite its extensive developmental and functional unit, it refrains from regeneration after major injury. Damage to the brain resulting from trauma, stroke or neurodegenerative disorders could lead to a permanent loss of function and result in long-term, irreversible damage. Unlike other organs in the human body, such as liver or skin, which have the potential to substantial repair and complete regeneration the human brain is incapable of restoring structurally post damage. Although a genetic blueprint that guides the brain development in the neural cells of adults, nonetheless, this potential is not re-activated naturally following damage, thus resulting in a fundamental biological paradox. Research over the decades pronounces this paradox, illuminating the presence of adult neurogenesis. Certain regions of the brain – like, hippocampus and the subventricular zone – retain certain numbers of neural progenitor cells, – which have the ability to develop into new brain cells (neurones), they are found in the hippocampus (includes memory and learning) – which have the ability to produce new and profound neural connections throughout life. This process is known as *Neurogenesis* (Gage, 2003). This capacity of ongoing neurogenesis questions the notion of the adult brain being a static, post-mitotic organ. Yet, this process is spatially limited, regulated and not sufficient to restore function lost due to trauma, disease or damage. Biologically, this research challenges the regulation of gene expression and cellular behaviour in neural tissues; Medically, it presents itself as a barrier to treating stroke, brain trauma or even degenerative conditions – like Alzheimer's. Finally, we come to the prime focus for the research paper, of why despite having the ability to retain the genetic capacity for repair, the adult human brain refuses to activate functional regeneration after injury. This is a theoretical paper, and would be looked at with a literature-based lens, which will consider recent findings in neurobiology, and prominent tissue engineering to explore the cause of the human brain to hold back from regenerative activity.

3. THEORETICAL ANALYSIS

Despite the fact that necessary information regarding tissue repair is embedded in the DNA of adult brain cells, the process remains dormant. Unlike some organs – like, the liver or skin – that can regenerate damaged tissue cells, the brain forms scar tissues that don't restore the lost neurones and synaptic connections. Yet the required genetic information that directed the brain development during embryogenesis remains present in the adult brain. This major disconnect between the potential and outcome is one of the most consistent questions raised in neurobiology. When the brain undergoes early development, a number of neural progenitor cells are formed, which are guided by accurately structured molecular signals and an environment flexible for plasticity. Several factors, including growth, and the abundant number of stem cells, help in the formation of an organised neural network. However, once the brain reaches a mature stage, the capacity for it to regenerate drastically shifts. The environment of an adult brain becomes inhibitory to cell division, and protective mechanisms dominate the adequate response to injury.

According to recent studies, the process of neurogenesis does occur in the adult human brain but is limited to specific areas. Therefore after a traumatic event, like a stroke, researchers have observed some neurogenic activity, but not enough to replace damaged tissues or restore complete function. Cell migration and integration can be significantly discouraged due to contributing environmental and molecular factors – molecular inhibitors, such as Nogo-A, a reduced number of naturally occurring or endogenous stem cells, and an extracellular environment.

3.1 comparing physiology

As a matter of fact, the brain is not the prime organ with the disability to regenerate itself. The heart also displays poor tissue repair post injury; but unlike the heart, the brain inhibits inherent potential to regenerate through neurogenesis, giving it a higher cellular and structural form of diversity. Additionally, unlike other organs with a rather simpler structure, the brain's intricate and complex circuitry cannot be repaired by simply regaining lost cells; a proper integration is required for adequate functional recovery. These adverse factors don't only make the brain biologically intriguing but also clinically urgent as a subject for research on regenerative capacities.

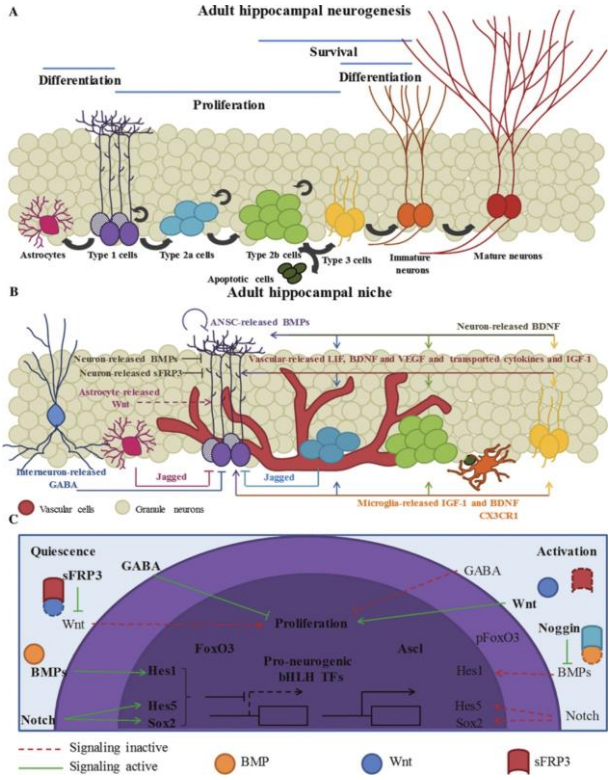

Fig 1.1 https://www.researchgate.net/figure/Adult-hippocampal-neurogenesis-under-physiological-conditions-A-A-schematic-diagram_fig1_319486133

Figure 1.1 shows how new brain cells are formed, through a series of stages. It begins with stem-like cells and ends with completely developed neurones. Along the process, several signals from nearby brain cells facilitate the process. They, like GABA, tell the cells when to grow, divide or become neurones. Many comparative biological researches on regeneration, show that certain species – like the zebrafish and axolotls – can regenerate almost the entire portion of the Central Nervous System (CNS). These vertebrates are capable of activating pathways known as the latent developmental pathways in response to injury, a process that mammals conveniently suppress (Diotel et al., 2020b). In these species, neural regeneration is primarily driven by the expression of the gene, SOX2 – which is a transcription factor that is critical for the maintenance of neural stem cell (NSC) identity and promoting the process of neurogenesis. Vertebrates show a high level of this transcription factor, and are expressed in numerous neurogenic zones throughout a lifetime. However, mammals show an appearance of this gene only in particular regions – like the hippocampi and the subventricular region – and it gradually decreases with age or traumatic events. Therefore, also reducing the renewal of stem cells and neural regeneration.

Another regulator which plays a key role in this is the Notch Signalling Pathway, which is significantly downregulated in vertebrates, like zebrafish, following injury to the central nervous system (CNS), this allows the activated stem cells to differentiate and regrow tissue. On the other hand, in the adult brain of a mammal, these numbers tend to be elevated, hindering reparative neurogenesis.

Similarly, the activation of the Wnt/ß pathway– a signalling pathway involved in various cellular processes – plays a crucial role in the promotion of neural progenitor cells multiplying and increase the number of cells that can differentiate into glial cells and neurones, also commonly known as neural progenitor proliferation (Makrygianni & Chrousos, 2023) and guiding neural circuits that are injured, in zebrafish. Wnt signalling – a pathway for cell communication, involved in a variety of developmental processes and homeostasis in adult tissue – is amplified in regenerative species to support their axonal regrowth and synaptogenesis, – process of forming new synapses – post-injury. However, in humans, Wnt activity is suppressed due to inflammatory cytokines that follow brain damage, therefore drastically reducing neurogenic potential and successfully impairing recovery (Labusch et al., 2020).

3.2 neurogenesis in other brain regions

While research suggests that neurogenesis occurs in two key regions in the brain, – the subventricular region of the lateral ventricles and the subgranular zone of the hippocampus – extended research also shows how the potential for the brain to regenerate extends beyond these regions. Under pathological conditions, where patients suffer through ischemic stroke or a severely traumatic brain injury, there have been multiple signs of potential neurogenesis in areas like the striatum, and to an even lesser extent, the cerebellum. According to the article published by Cerminara et al. (2015b), in the striatum, especially after a stroke, neural progenitor cells that originate in the subventricular zone, can potentially migrate to the site of injury. Over here, some cells differentiate striatal neurones. Even though most of these neurones fail to integrate completely or simply survive and are short-lived, the mere presence of the process, neurogenesis, challenges the long-standing belief of the human brain incapability to regenerate or undergo meaningful repair.

Cerebellum, commonly viewed as a non-neurogenic zone, – an area where neurones are absent – has also shown occasional regenerative activity. Reliable research done on rodents, indicate that the glial cells present in the cerebellum, specifically the Bergmann glia, – these play a major role in the development and function of the cerebellum – may acquire properties that are similar to neural progenitor cells, post-injury, resulting in the production of new neurones or glial intermediates. In spite of the fact that this process is more active in neonatal mammals, some evidence suggests how in adult mammalian brains, the cerebellum is capable of responding to damage, even if with limited plasticity. The complexity of the brain, structurally, and its mature circuitry present in the cerebellum make the constraint to the regenerative process, obvious. Most neurones that are newly generated do not survive the environment post-trauma due to protective measures taken by the brain, like, glial scarring, inflammation and various inhibitory molecular cues. Several molecules, such as, Nogo-A (which acts as a potent inhibitor of neurite outgrowth and regeneration in the CNS), MAG (myelin associated glycoprotein found in the nervous system), and OMgp are expressed in adult central nervous system tissue and acts as a suppressor for axonal growth and formation of neurones.

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